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OBITUARY

JOSHUA LEDERBERG (1925 – 2008)

The foundations of molecular biology were laid in 1940's and Joshua Lederberg was one of its prominent, prodigious and prolific architects. He single-handedly established the science of bacterial genetics. The academic life of Joshua Lederberg is replete with elements of precocity, opportunity, failures, determinism, successes, administrative and societal responsibilities.

Joshua was born on May 23, 1925 in Montclair, New Jersey. His precocity and preoccupation with science expressed itself when he wrote at age of seven that he wanted to be 'like Einstein' and to 'discover a few theories in science'. Early intellectual prowess made him lonely for want of 'intellectual sparring partners' and his adolescent years were spent in the safety of New York Public Library. He read everything: the story of Robert Koch and Louis Pasteur described in Paul de Kruif's book *The Microbe Hunters* inspired him sufficiently to direct his attention towards medical research.

After graduation at the age of fifteen, Joshua enrolled for Zoology major at Columbia University in 1941 where his teacher and mentor Francis Ryan infused a degree of control over his ravenous and uncontrollable mind. After acquiring Bachelor's degree in Zoology in 1944, he decided to pursue medical career but continued to conduct experiments under Ryan's supervision. After a few failed experiments Ryan suggested him to take one year leave from medical curriculum to work with Edward Tatum at Yale who was an expert with *Neurospora*. One year extended to life long engagement with research and changed genetics forever: in 1958, at age of 33 years Joshua Lederberg was awarded the Noble Prize along with Edward Tatum and George Beadle.

Lederberg's experiments are best appreciated in the light of then prevailing academic knowledge and wisdom. Bacteria were then thought to be too primitive for studying classical genetics and it was assumed that bacteria multiplied by cell division such that the progeny was genetically indistinguishable from the parent. In 1944 Avery dented the classical wisdom by identifying DNA as the transforming material in *pneumococcus* bacteria. Lederberg tried to look for DNA mediated transformations in the *Neurospora*. But his experiments failed because the *Neurospora* mutants lacking the ability to synthesize leucine, that he chose, underwent spontaneous mutations during the course of experiments. Far from being discouraged, he later showed that the spontaneous acquisition of leucine synthesizing ability by the mutant was caused by reverse mutations that were allelic to the mutation. The reverted mutants were called 'prototrophs' by him. He established the method of identification and recovery of prototrophs and developed the technique of using selective growth media

widely used in microbiology today. Given his insatiable mind, he decided to the check DNA mediated transformation in bacteria, and whether the bacterial multiplication involved genetic recombination. He chose two mutant strains of the *Escherichia coli* (*E coli*) each with inability to synthesize either methionine or proline. He carried out crossing experiments to obtain recombinants that had inability to synthesize both the amino acids. Even if he could find one such bacteria amongst the billions, it would prove that bacteria exchanged genetic material. His was unsuccessful in finding 'the one', simply because the strain of *E coli* that he chose was sterile. Then he used double mutant *E Coli* from Tatum's K12 strain. Double mutants did not synthesize two amino acids each and it decreased the chances of spontaneous reversion as seen in *Neurospora* previously. Lederberg observed that multiplying bacteria reacquired the ability to synthesize the amino acids when two strains were incubated together but not when each strain was incubated separately. He also noted that all the bacteria in each colony were identical and the trait was inheritable. This was an evidence of exchange of genetic material between bacteria by a process he named 'conjugation'. He repeated the experiments several times to ensure that it is not due to chance factor. Along with nutritional properties he also isolated bacteria with differential resistance to bacteriophage T1, and concluded that that bacteria had only one chromosome (haploid). He completed his crossing experiments in six weeks and the results were exciting enough to extend his leave from medical college to submit his work for Ph. D. in 1947. Effectively he proved that the principles of classical genetic apply to bacteria as well and that bacteria can be used as system for experiments with an added advantage of simplicity and rapid multiplication.

When his was about to join back to continue medical education, he was offered an Assistant Professorship in Genetics at Wisconsin, Tatum's *alma mater* at the age of 22. He gave up the medical career for an opportunity to work in basic genetics. He continued his association with *E Coli* for many years and worked out linkage map of the chromosome, however his systematic alliance with *Salmonella* (chosen due to its virulence) led to the discovery of transduction and plasmids. His team had pioneered the use of antibiotic resistance in bacteria as genetic marker along with nutritional requirement to identify the strains that were fertile. He developed 'replica plating' as a high-throughput method of identifying mutants with bacterial resistance. He proved that bacterial resistance was transferred by genes, and this method has been widely used for studying genetics of bacterial resistance.

In 1951, Lederberg and Zinder decided to undertake a reverse test to examine the conjugation as means of transfer of genetic material between bacteria. They developed a U-tube and put two different strains of *Salmonella* on either side separated by a filter that allowed molecules to pass but not the bacteria. The medium was moved sufficiently across the filter to ensure adequate mixing. They expected no transfer of characters. Like always, something else happened. The strains acquired each others characters. Systematically they could negate either DNA or RNA as the transfer agent by use of lytic enzymes. Eventually they found that the agent of transfer was a bacteriophage virus. It was a lytic virus; as the bacteria was about to lyse, the viral assembled random portion of genetic material of bacteria into its genetic core. The viral could pass through the filter and then infect the other strain to release its genetic information along the acquired DNA from the previous strain. The phenomenon of transduction has changed the way the power of viruses could be

harnessed, and is being used for genetic manipulation of the DNA of virtually any cell. It also explained the quick development and transfer of resistance amongst bacteria.

Lederber also discovered plasmid as an extrachromosomal genetic material that carried genes for proteins not required for growth. Plasmid since then have been used for genetic engineering with mass production of human insulin in 1970's by insertion of human insulin gene into bacterial plasmid and many other recombinant products for experimental and medical use.

In 1957, Sputnik was launched by Soviet Union. True to his nature, he entrenched himself in literature on astronomy and rocket science. In his letters to reputed journals he expressed his concern about the chance of bringing in infectious alien microbiological material from space into earth against which there is no natural immunity. His concerns found an echo in NASA think tank and procedures for strict quarantine were adopted for all space missions. He developed the computer controlled biomedical laboratory for Mars Mission examination of Martian soil for proof of life. His stature and stance on extraterrestrial life forms popularized space exploration that found place in numerous fictional material as well as motion pictures. Lederberg worked for NASA as consultant from 1961 to 1977. While working on automated laboratory he recognized the potential application of computers in biomedical research and developed algorithm for a computer program called DENDRAL along with computer expert Edward Feigenbaum and chemist Carl Djerass for determination of molecular structure of unknown material in 1965. Through DENDRAL, he brought artificial intelligence to operation level in research in biomedical sciences.

Lederberg established the Department of Genetics at University of Wisconsin and his appointment as the first Chairman of Department of Genetics at Stanford University at the age of 33 started a long list of administrative responsibilities at Wisconsin, Stanford and Rockefeller Universities. Beginning at 1960's, he remained advisor to the nine US Government agencies in different capacities on policy matters relating to health, medical research, emerging infectious diseases, space exploration, biological warfare, national security and arms control. He shied from public spotlight but tried to improve communication between scientist, policy maker and public in many ways including a weekly column on *The Washington Post* for several years.

In his own words, Joshua was always curious about new things, wanted to go into field that haven't been investigated and finding new approaches to it and he was never inhibited by the fact that he did not know something about a subject. He advised the young: "Try hard to find out what you're good at, and what your passions are, and where the two converge, and build your life around that."

Johsua Lederberg breathed his last on February 2, 2008.

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